THE SECRETS OF LONG LIFE FROM LONGITUDINAL DATA

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Abstract

In this paper we perform analysis of extreme longevity using longitudinal data collected in Framingham Heart Study (FHS). For these purposes we identified sub-cohorts individuals (males and females), having potential to live long life. We evaluated age trajectories of physiological indices for these sub-cohorts and compared them with those for the rest of FHS participants. We found that average trajectories of such indices as well as survival curves in these groups of individuals differ significantly. Then we developed mathematical and computer model of human mortality and aging appropriate for the analysis of longitudinal data and evaluated dynamic characteristics of risk functions. We found that the notion of "normal" physiological state (corresponding to minimal risk) depends on age and estimated respective age trajectories. The relations between the dynamic properties of risk functions and changes in stress resistance with age are discussed.

Introduction

In addition to data about individuals' life spans, traditionally collected in demographic studies, longitudinal studies of aging and longevity collect information about age trajectories of physiological variables, such as body mass index, level of serum cholesterol, pulse pressure, etc. How can this information be used in the analysis of extreme longevity? Do trajectories of long-lived individuals differ from those who died prematurely? If they do, can this difference have something to do with the difference in the rate of aging between short-lived and long-lived individuals? Gerontologists and geriatricians know that empirical notion of "normal" physiological state has different meaning for individuals of different age. This is because human organism experiences age related changes in physiological functioning. Although this fact is recognized and widely used in medical and epidemiological practice the theoretical aspects of this notion are not well elaborated. Is there a formal way to evaluate the age trajectory of the "norm" using appropriate data? Can the "normal" physiological changes be associated with some relatively stable age patterns, observed in long-lived individuals, or is the age pattern itself not as important as the range of deviations from the mean at different ages? It is also unclear, how individual differences in physiological functioning can be reconciled with the average "norm" typical of respective age. It is also unclear how informative are data on age trajectories of physiological indices for survival outcomes. Do individuals whose physiological state follows the "normal" age trajectory have the longest life spans, or the long livers have special age trajectories of physiological indices different from other individuals died prematurely? The longitudinal studies of aging and longevity, which include measurements of physiological state, can be used to address these questions. In this paper we use Framingham Heart Study (FHS) data to address these questions.

Individuals with and without potential to live long life

To compare age trajectories of physiological indices for the long lived individuals with those having short life we evaluated the empirical distribution of life span among participants of the FHS cohort and defined individuals with exceptional life span as those who had survived 83 years for males and 86 years for females. Males deceased before age 70 and females deceased before age 73 were included in the group of short-lived individuals. Then we evaluated age trajectories of body mass index for the two groups and for each sex. Note that mortality rates for selected groups of long-lived and short-lived FHS participants are incomparable because they are defined different parts of the entire age interval characterizing the life course of the FHS cohort. For example, for the short-lived males this interval is between 47 and 70 years. For the long-lived males the mortality rate is defined starting from age 83. This excludes individuals who died between 70 and 83 years of age from the analysis, and makes comparison of mortality rates among selected groups impossible.

To make survival characteristics in the two groups comparable one needs to slightly modify the definitions of respective groups. It is realistic to assume that some individuals having potential to live long lives died prematurely, probably because of extreme external conditions, and vice versa, that some potential short-livers managed to live a long life because of favorable conditions. Thus to be able to evaluate mortality rates and survival functions at the entire age interval we need to divide male and female FHS cohorts into two sub-cohorts of individuals. One includes FHS participants having the potential to live a long life. Another consists of FHS participants who do not have such a potential.

Such a division has been performed for male and female parts of the FHS cohort using methods of cluster analysis in the space of physiological trajectories, taking into account details of physiological dynamics in the groups of long-lived and short-lived individuals selected above. For example, individuals were considered to be potential long-livers if trajectories of their physiological indices were close to respective trajectories of long-lived individuals selected above. As a result, the entire FHS cohort becomes separated into four sub-cohorts. The results of such an analysis for males are shown in Fig.1.

Fig. 1. Average age trajectories of body mass index (left), levels of serum cholesterol (middle), and pulse rate (right) for the long-livers (filled dots), and short-livers (open dots), males. The solid and dotted lines correspond to the age trajectories of respective indices produced by quadratic hazard model for the long-lived and short-lived male FHS participants respectively.

One can see from this figure that the age trajectories of physiological indices for potentially long lived and short lived individuals differ substantially.

Survival functions

Fig. 2 shows survival functions for the groups of potential long- and short-livers respectively. One can see a substantial difference in survival between the groups. The estimates of models parameters allow for evaluation of differences in dynamic mechanisms describing age related changes in physiological state.

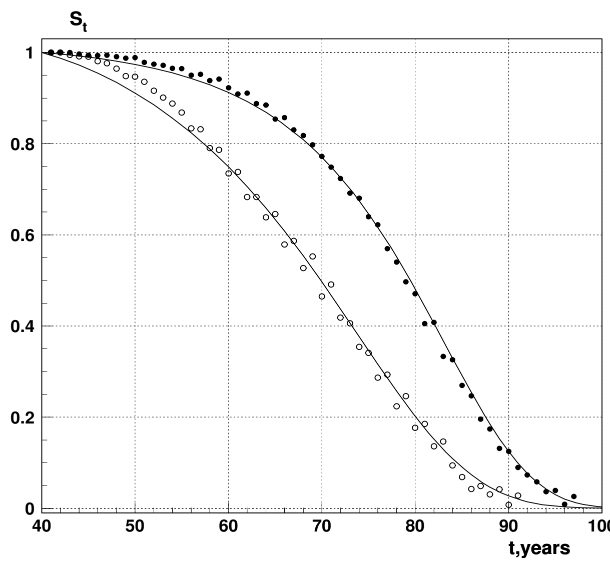

Fig. 2. Empirical survival functions for the groups of potential long- (filled circles) and short- (open circles) livers in the FHS male cohort and their predictions calculated using quadratic hazard models.

Modeling dynamics of physiological state

We developed a stochastic process model of human mortality and aging where we explicitly described the "norm" as the value of physiological indices corresponding to minimum value of risk function (Fig.3). We fitted this model to each of four FHS sub-sets of data and estimated the models' parameters for the part describing physiological dynamics, and the part related to mortality rate including parameters of stress resistance.

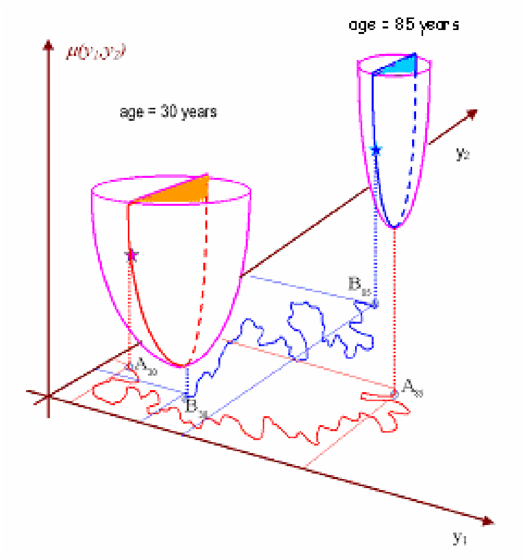

Fig. 3. Risk of contracting disease as a quadratic function of hypothetical risk factors (physiological indices) at ages 30 and 85 years. Individual “B” has a minimal risk at age 30 years. However at age 85 years its risk is higher than minimal. The risk of individual “A” at age 30 is higher than minimal. However, its risk at age 85 has minimal value.

Conclusions

The analysis of the FHS data shows that each of the FHS male and female sub-cohorts can be successfully separated into two sub-cohorts consisting of potential long- and short-livers, respectively. These group of individuals have substantially different average age trajectories of physiological indices. A quadratic hazard model with constant coefficients regulating physiological dynamics captures basic dynamic properties of trajectories of selected physiological indices, as well as regularities of survival in each group. The results allow us to conclude that the “normal” physiological state changes with age, and that the values of risks, risk factors as well as shape of risk functions associated with values of physiological indices change with age.